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The Genetics of Hypopituitarism

Should we do genetic testing in patients with hypopituitarism?

Sally Radovick, MD
Professor of Pediatrics, Senior Associate Dean for Research
Rutgers–Robert Wood Johnson School of Medicine

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Hypopituitarism in children presents with short stature

- Height or length below the 3rd percentile on standard growth curves
- Height-for-age >2 SD below the mean for gender (2.3% of all children)

SD = standard deviation

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Genome Wide Association Study (GWAS)

180 genetic loci have been shown to influence only about 10 % of the phenotypic variation in adult height.

Hirshhorn JN. et al. Nature 467, 832–753 (2010)

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SNP in IGF1 determines size in dogs

A single IGF1 single-nucleotide polymorphism haplotype is common to all small breeds and nearly absent from giant breeds, implying that sequence variation in the *IGF-1 gene plays a causal role in dog* size.

Sutter NB, Science. 2007; 316:112-5.

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Normal variants ? Genetic

1. Familial short stature
   - Short stature in family
   - Normal growth rate, age of puberty and bone age

?

2. Constitutional delay of growth
   - Can reach normal height
   - Normal growth rate
   - Delay in age of puberty and bone age
   - Often has familial pattern, especially in males

?

3. Idiopathic short stature
   - Growth rate <50 percentile for age
   - Normal or slightly delayed bone age
   - Target height below mid-parental (some reach midparental target height)
   - Normal IGF-I, IGFBP3 and GH response to provocative testing
   - Heterogeneous group; includes SGA

?

IGF = insulin-like growth factor; IGFBP = IGF-binding protein

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Pathologic variants

1. Proportionate
   - Prenatal
     - IUGR
     - Chromosome abnormality
     - Dysmorphic syndromes
     - **Defects in pituitary development**
   - Postnatal
     - Malnutrition, Chronic disease
     - Drugs
     - Psychosocial dwarf
     - Endocrine disease
2. Disproportionate
   - Rickets
   - Skeletal dysplasia

IUGR = intra-uterine growth retardation

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Causes of short stature

- 353 patients with short stature
  - **50%** constitutional delay or familial short stature
  - **19%** chromosomal (primarily Turner syndrome and variants)
  - **3%** recognisable multiple malformation syndrome
  - **2%** endocrine

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Lam WFF *et al. Chin Med J* 2002:115;607–17

Diagnosis of GHD

- Auxiological
  - Height >2.25 SD below mean (or <3%ile)
  - Growth rate <50%ile for age
- Biochemical
  - GH is secreted in pulses
    - Random sample will likely be low even in normal patients
    - IGF-I is a screening test
    - Provocative testing is non-physiological
- **Genetic**

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GH Safety

- Sante Adulte GH Enfant (SAGhE)–Epidemiologic study of patients treated with GH.

  - France: 30% increased risk of death with hGH treatment compared to the general population, with 93 observed deaths in the treated group versus 70 expected. (bone tumors and cardiovascular diseases including cerebrovascular events)
    (published later as :Carel JCJ Clin Endocrinol Metab. 2012 Feb;97(2):416-25)

- Ongoing review by FDA and European Medicines Agency (EMA)

  - Belgium, Netherlands, Sweden: none of the patients died from cancer or from a cardiovascular disease.
    (Sävendahl LJ Clin Endocrinol Metab. 2012 Feb;97(2):E213-7)

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1. The definition of short stature remains auxiological since laboratory parameters are not always reliable in the diagnosis.
2. Treatment of short stature with GH is expensive and there are concerns regarding long-term safety.

A genetic understanding of short stature is desirable and genetic determinants of stature are becoming increasingly recognized.

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Evolving Congenital Hypopituitarism

Although pediatric endocrinologists have recognized that children with idiopathic hypopituitarism may develop additional hormone deficiencies, no systematic studies have looked at a mechanism of progressive hormone deficiency and which patients are at risk and require continued monitoring

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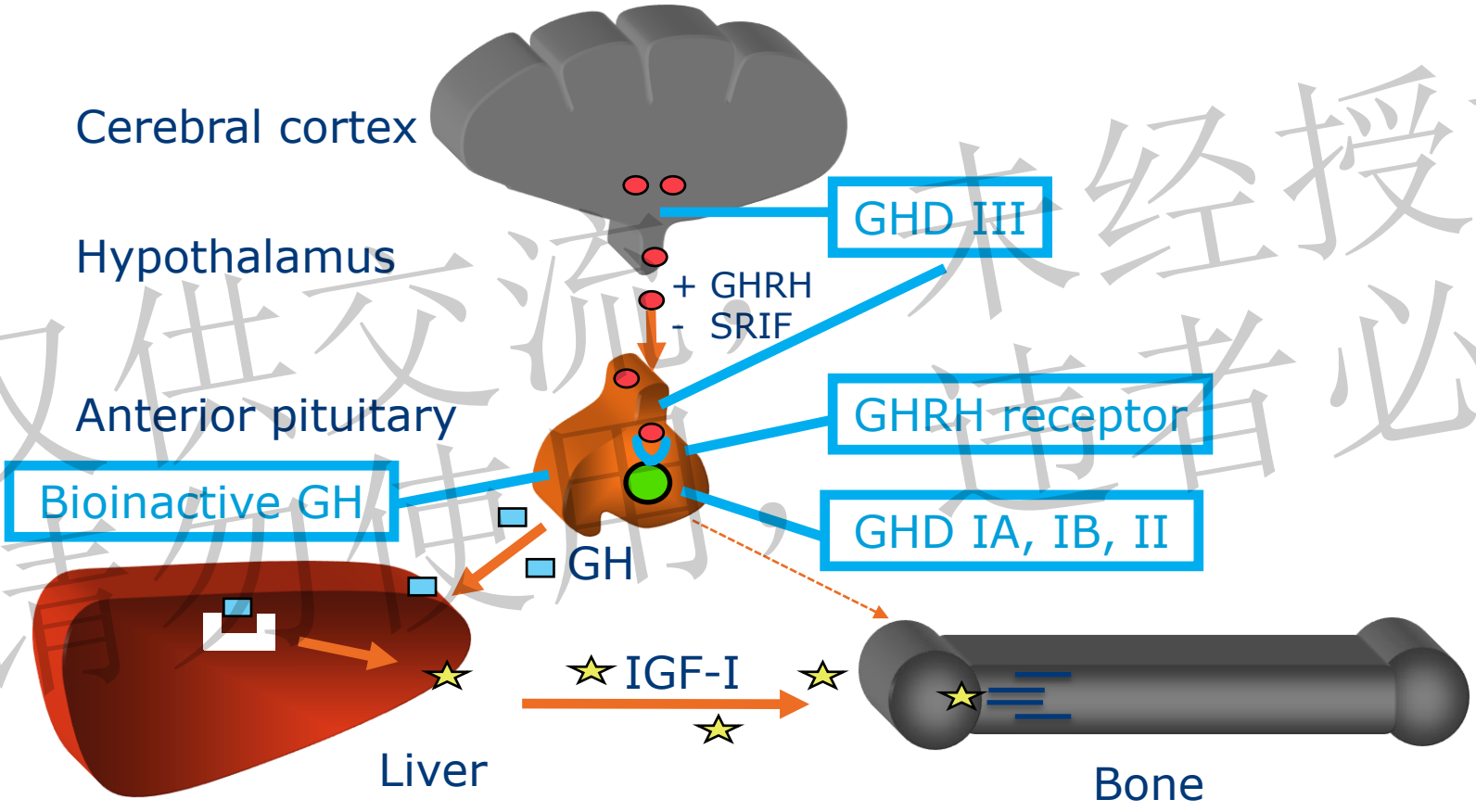
Mutations in the GH gene are rare



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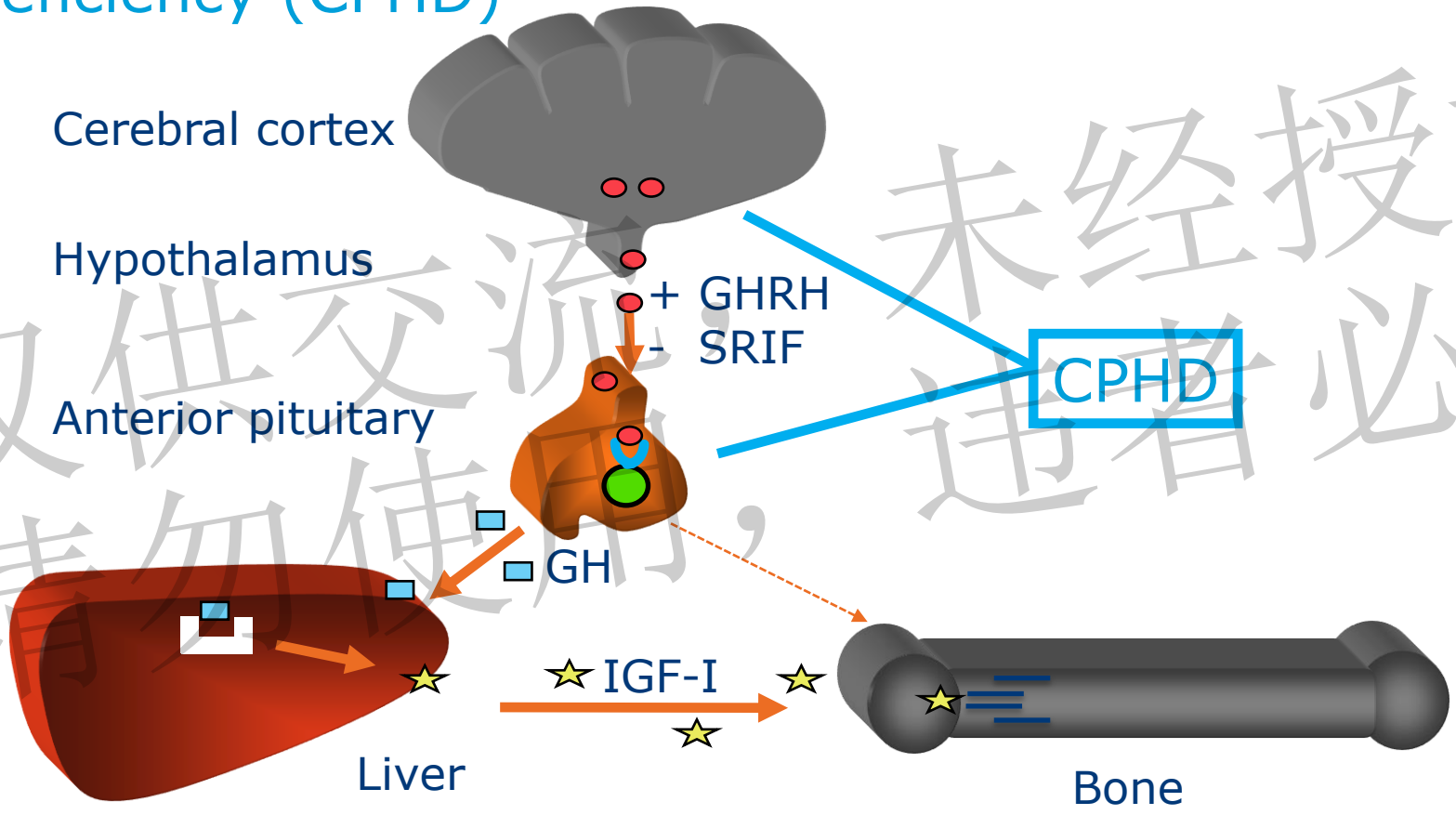
Combined Pituitary Hormone Deficiency (CPHD)



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Congenital hypopituitarism

- Hypopituitarism is not rare
  - Incidence rate: 4.2 cases per 100,000
  - Prevalence rate: 45.5 per 100,000
- Transcription factor mutations are not uncommon
  - 13.5% of 195 patients diagnosed with pituitary hormone deficiency had genetic mutations in the five analyzed factors
  - The prevalence increased to 52.4% when 21 familial cases were considered

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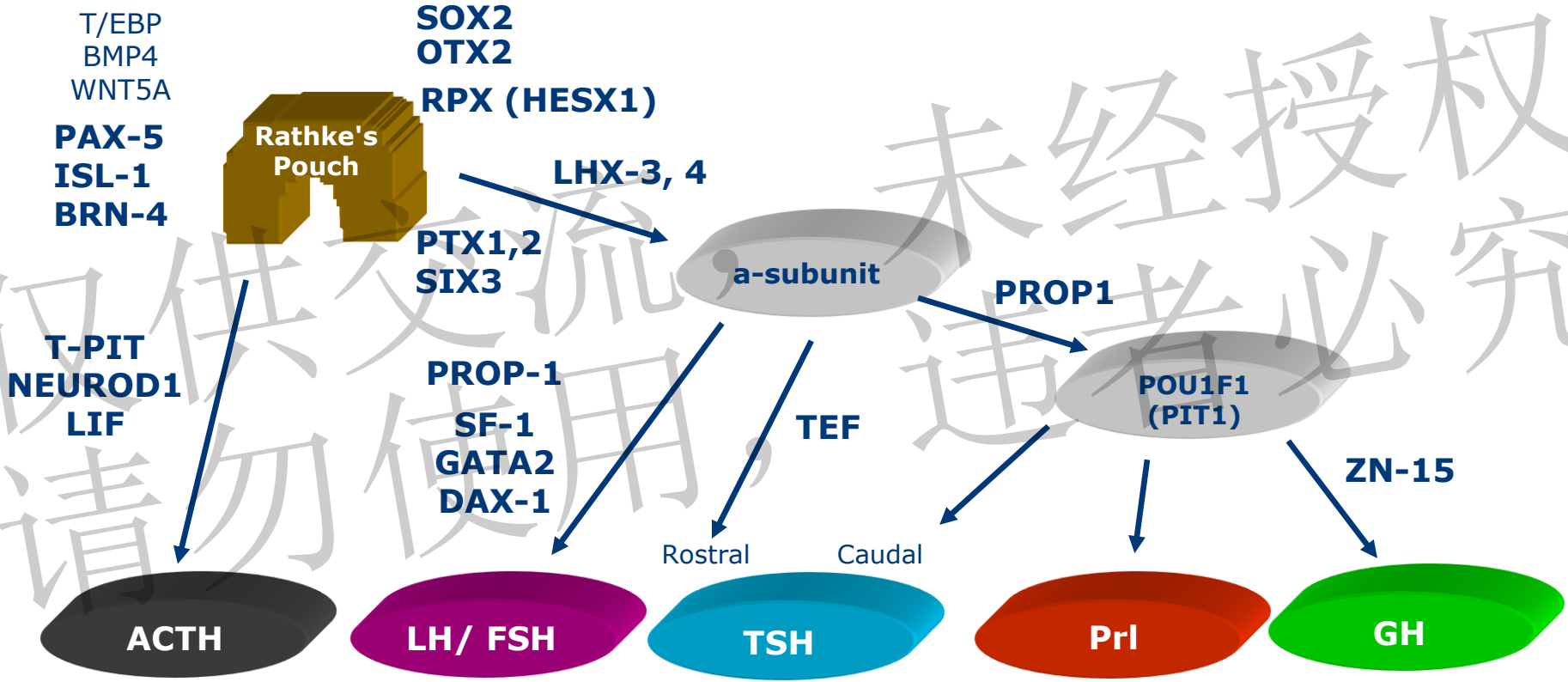
Reynaud R *et al. J Clin Endocrinol Metab* 2006;91:3329–36

Anterior pituitary development



ACTH = adrenocorticotropin hormone; LH/FSH = luteinizing hormone / follicle stimulating hormone

Romero CJ *et al. Trends Endocrinol Metab* 2009;20:506–16

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Management of congenital hypopituitarism

- Who should have genetic screening?
- How should they be screened?
- When should they be screened?
- Which patients should be monitored for evolving hypopituitarism?
- How should patients with hypopituitarism be monitored?

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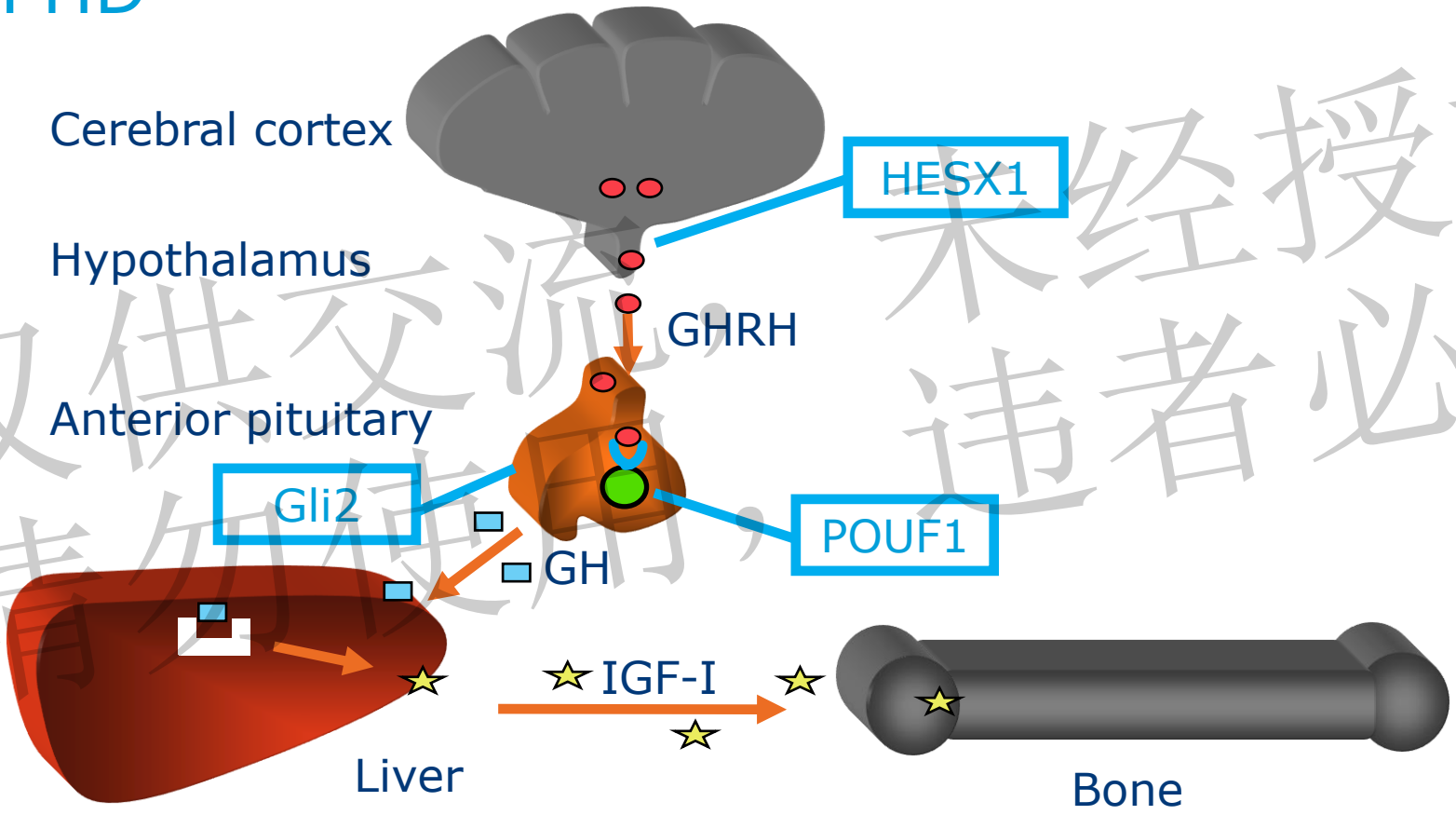
CPHD



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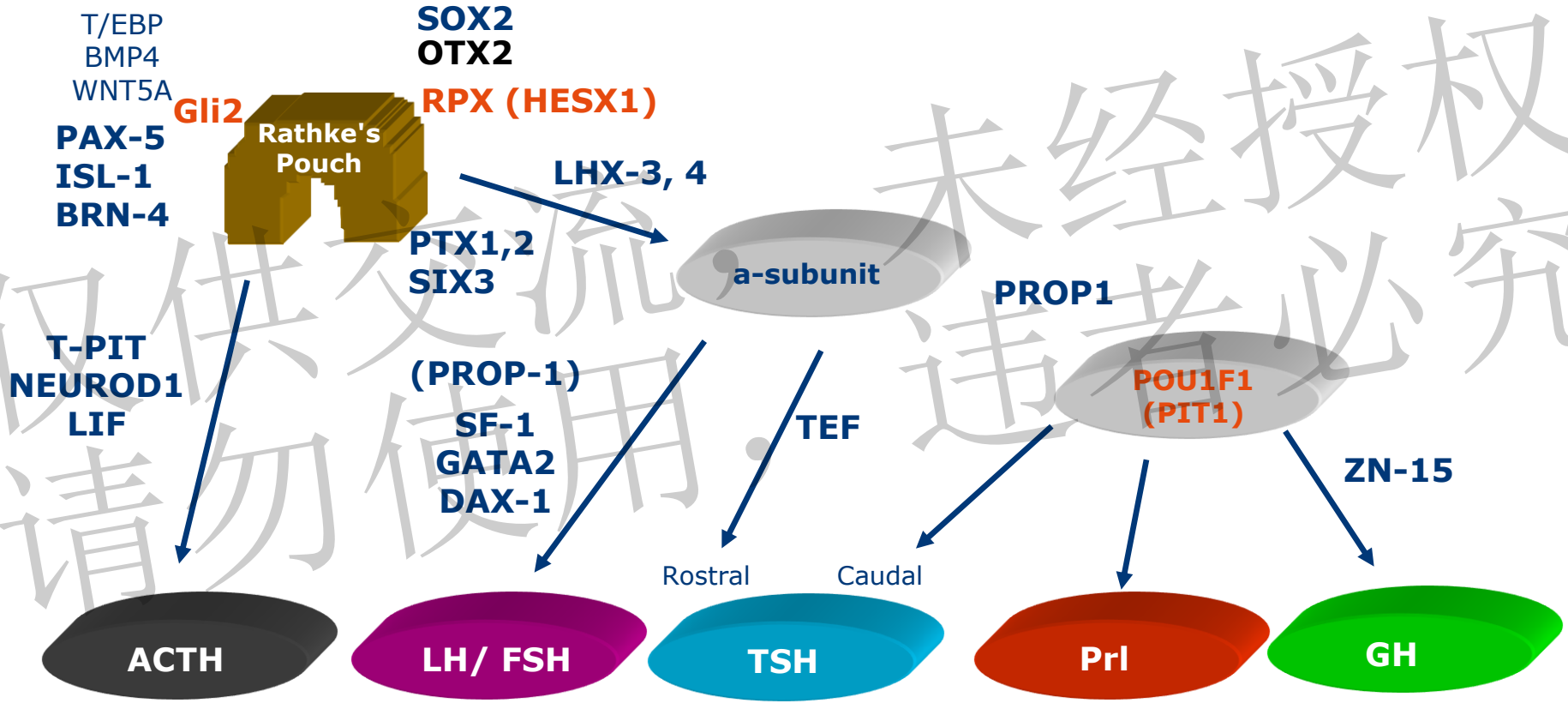

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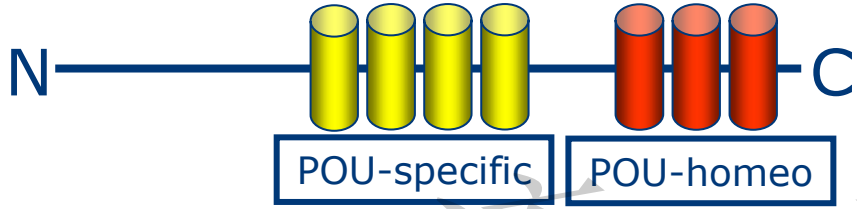
Romero CJ *et al. Trends Endocrinol Metab* 2009;20:506–16

POU1F1 (Pit-1)



- General
  - First cloned pituitary transcription factor
  - Member of the POU homeobox protein family
  - Contains a POU-specific and -homeobox domain required for DNA-binding and an activation domain in the N-terminus
- Clinical
  - CPHD (deficiency of GH, Prl, TSH)
  - Inherited as autosomal recessive or dominant

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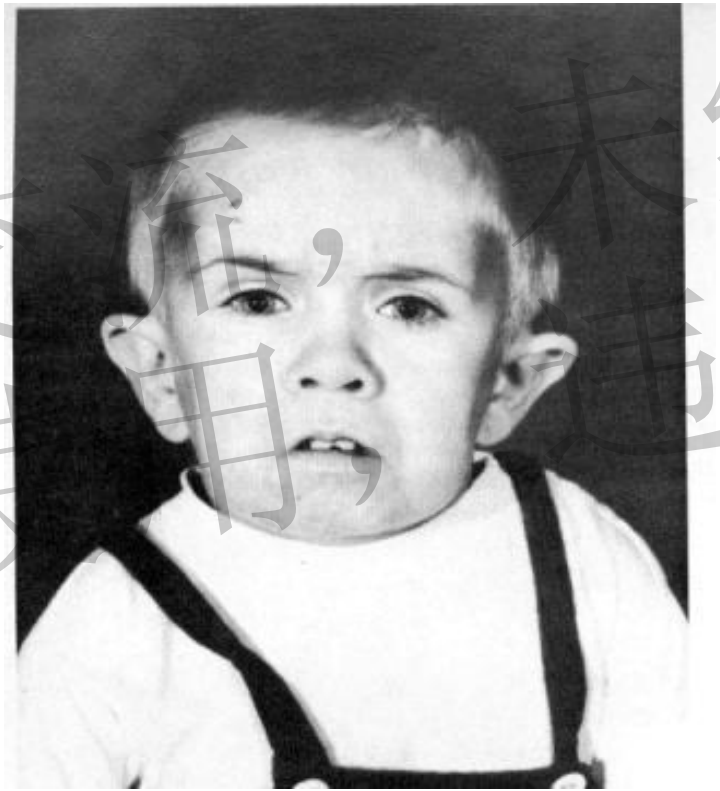
Cohen LE and Radovick S. *Endocr Rev* 2002;23:431–42

Patient WTR:
aged 10 years 4 months



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Patient WTR: history

- Severe mental retardation
- Short stature
- Undetectable GH
- Undetectable TSH
- Low Prl
- Normal cortisol response to insulin
- Normal gonadotropin response to GnRH

GnRH = gonadotropin-releasing hormone

Cohen LE and Radovick S. *Endocr Rev* 2002;23:431–42

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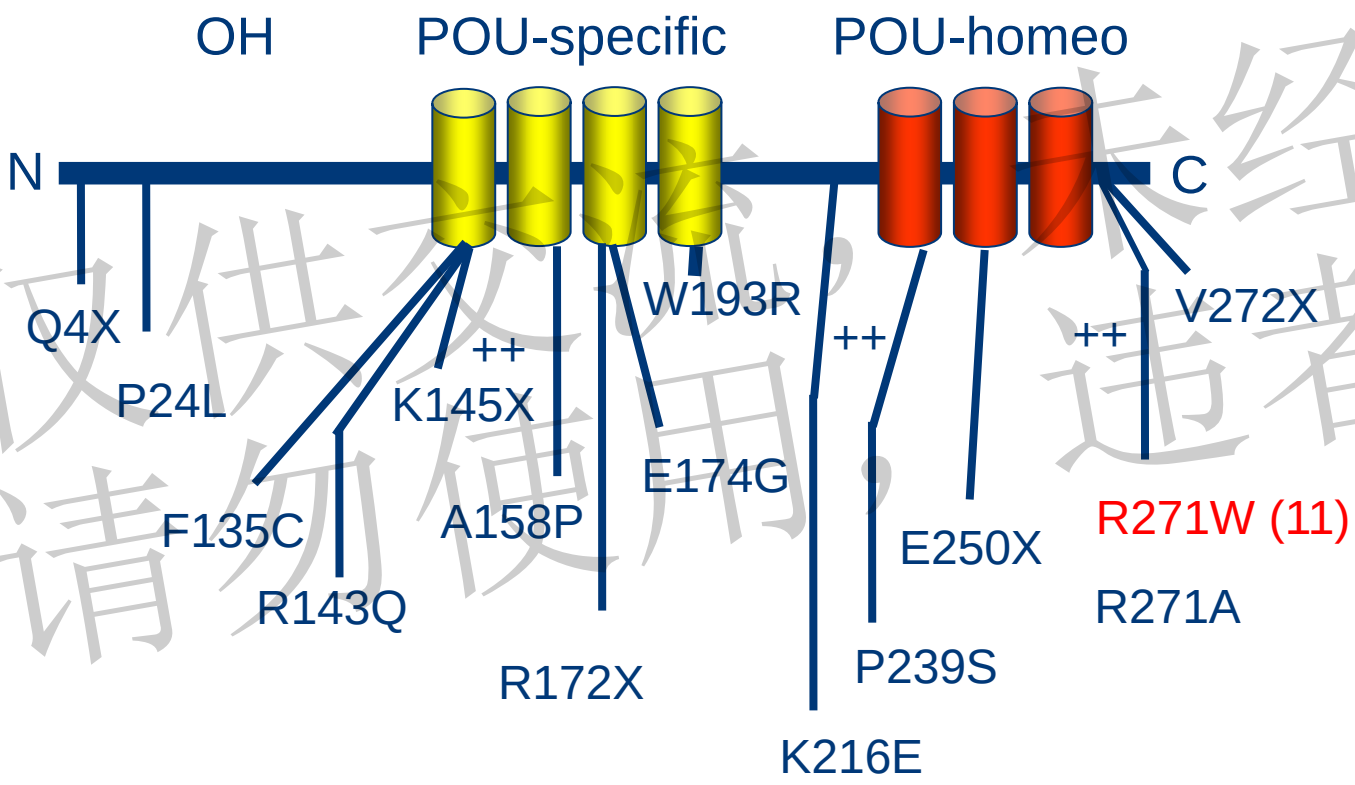
Human POU1F1 mutations



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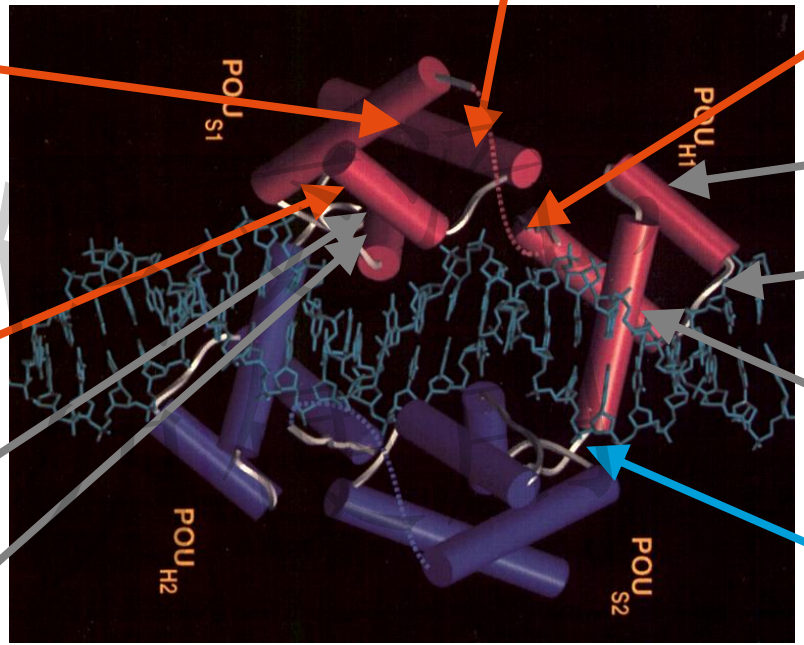

R143Q

K216E

F135C

E250X

P239S

A158P

W261C
(Snell mouse)

E174G

R271W
R271A

R172X

Jacobson EM *et al. Genes Dev* 1997;11:198–212

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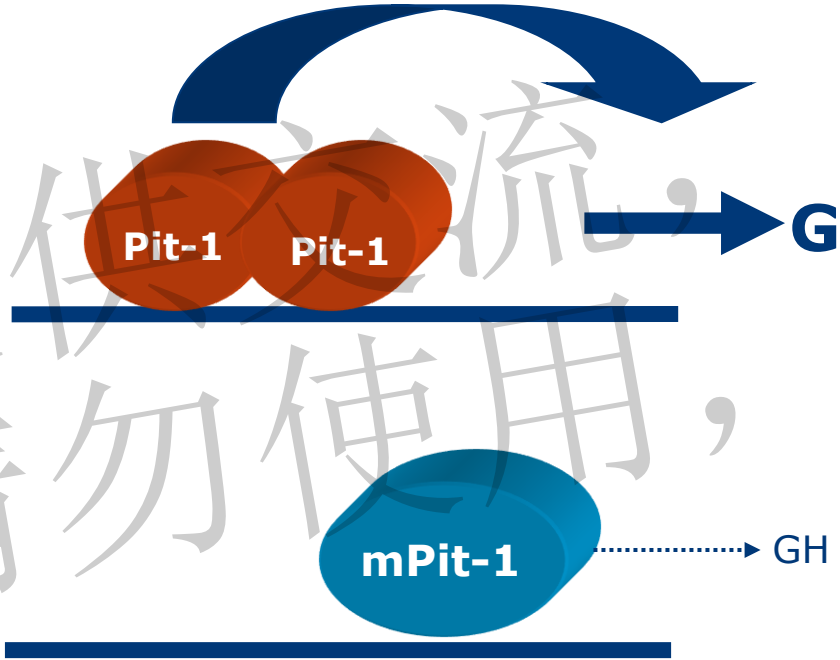
Model of dominant negative effects of Pit-1 mutants



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Combined pituitary hormone deficiency

- The mutations may be heterozygous and spontaneous with no affected family members
- Patients may present with GHD, and hormone deficiencies may evolve in patients with mutations in pituitary developmental factors
- Phenotype may not correlate with genotype
  - The anatomic abnormalities (i.e. pituitary hypoplasia and SOD) do not correlate with severity of the disease or the type of mutation
  - Developmental factors may be variably expressed in time and cell type to influence phenotype
- Can be vertically transmitted

SOD = septo-optic dysplasia

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Patient MR history

- Birth weight 2.9 kg, 36 weeks' gestation
- 'Prematurity' jaundice, normal neonatal screen
- Microphallus
- High-arched palate
- 2 months, CT normal
- 6 months, fall off in length and weight
  - GH provocative testing (GH max 1.4 mg/L)
  - Normal TFTs
- 22 months, TSH deficiency
  - T4: 39 nmol/L (58–193)
  - TRH test (TSH max: 1.7 mU/L; basal Prl: 5.4 mg/L, no increase)
  - MRI small pituitary

CT = computed tomography; MRI = magnetic resonance imaging;
TFTs = thyroid function tests; TRH = thyrotropin-releasing hormone

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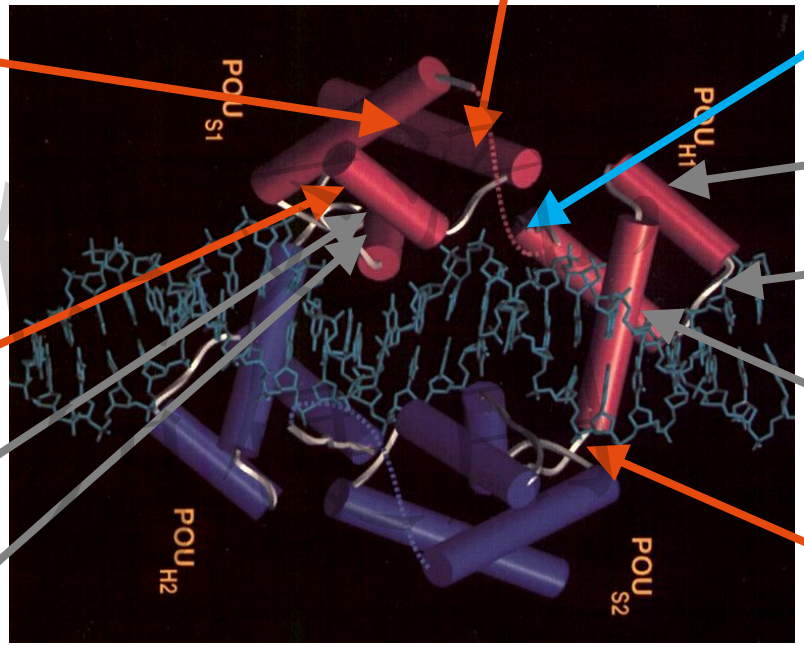
Human POU1F1 mutations



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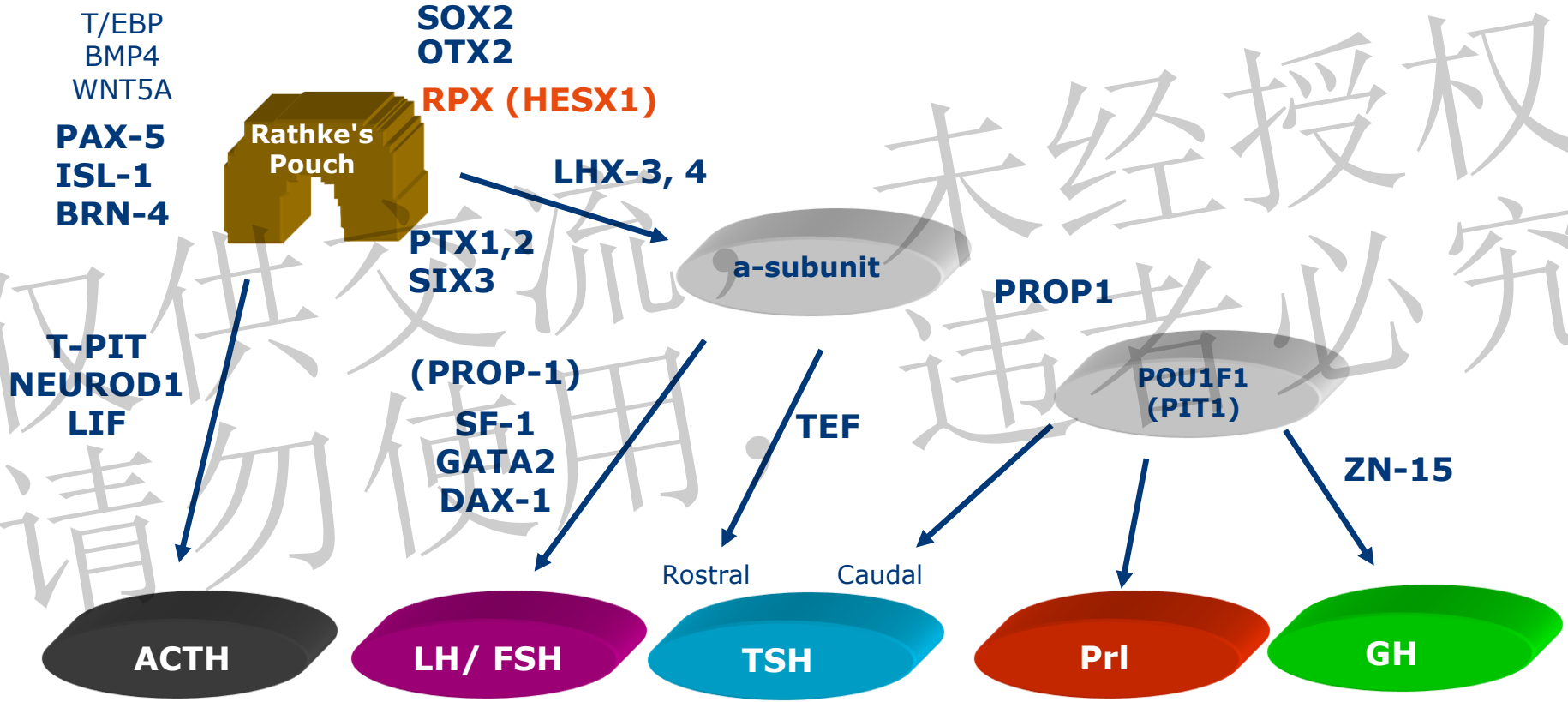

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Romero CJ *et al. Trends Endocrinol Metab* 2009;20:506–16

Patient JR

- 6 months: diagnosis SOD, blindness and nystagmus
  - MRI: absent corpus callosum, thin optic nerves, small anterior pituitary, absence of posterior bright spot
- 3 years 6 months: height: 98.2cm (–0.014 SDS); weight: 16.8 kg (+0.68 SDS)
  - IGF-I: 50 ng/mL (17–28); bone age: 4 years
  - TFTs normal; no DI; ACTH stimulation 18.0 mg/dl (5–21.7 mg/dL)
- 4 years 9 months: decreasing growth velocity (2.2 cm/year)
  - IGF-I: 22 ng/mL; TFTs normal; TRH test normal
  - Insulin stimulation: GH 4.2 mg/L; cortisol: 20.8 mg/dL
- 6 years
  - TSH: 0.13mU/L; T4: 4.4 mg/dL (6–12.3)

DI = diabetes insipidus; SDS = standard deviation score; TFT = thyroid function test; TRH = thyrotropin releasing hormone

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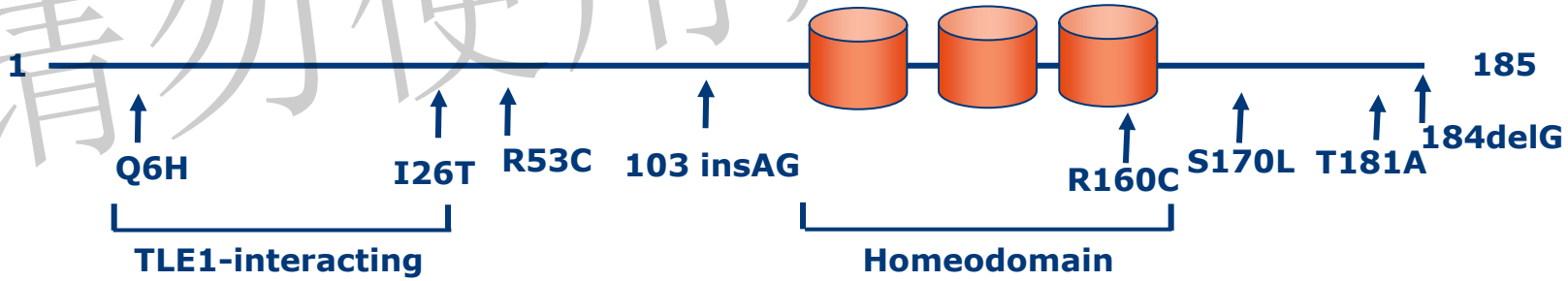
RPX (Rathke's pouch homeobox) or HESX1

- Earliest known pituitary gland marker, restricted to Rathke's pouch
- Rpx expression is repressed later in development
- SOD with absence of optic nerves, corpus callosum and panhypopituitarism
- Heterozygous or homozygous mutation with GH, TSH, Prl and LH deficiencies; ACTH deficiency reported



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Patient SK

- 20-year-old female post partum, unable to lactate
- Newborn with hypoglycaemia and jaundice
- Hypothyroidism noted at 6 months of age and treated with levothyroxine
- Poor growth: diagnosed with GHD at 16 months (0.9 ng/mL post-clonidine) and treated with GH until 16 years
- Normal puberty
- Normal pregnancy, TFTs monitored

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Pine-Twaddell E *et al. Thyroid;* in press

SK TFTs during pregnancy

- 13 weeks
  - TSH: 0.058 mIU/mL; T4: 7.8 mg/dL (4.5–12.0); FT4: 0.8 ng/dL (0.61–1.76)
- 17 weeks
  - TSH: 0.067 mIU/mL; decreased levothyroxine
- 21 weeks
  - FT4: 0.44 ng/dL (0.61–1.76)

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FT4 = free T4

Pine-Twaddell E *et al. Thyroid;* in press

JAK: son of SK

- 36-week newborn
- Neonatal hypoglycaemia
- Undetectable TSH
- Undetectable GH
- Normal cortisol
- Normal gonadotropins
- Family history
  - Mother treated with T4 and previously with GH

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JAK interval history
Age: 9 months

- Normal brain MRI
- Bilateral hearing loss
- Developmental delay
- Continues on levothyroxine, begun on GH

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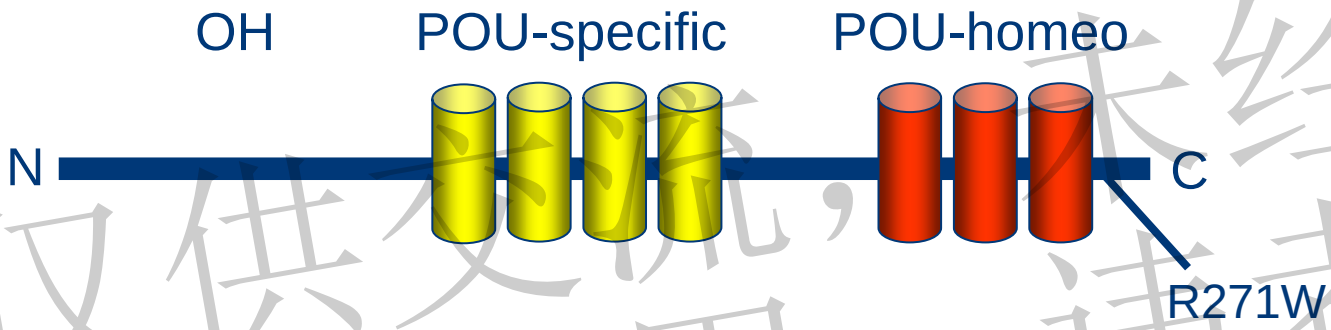
JAK and SK Pit-1 mutation



Vertical transmission of a dominant negative POU1F1 gene mutation with newborn sequelae

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The future of genetic screening for hypopituitarism

- Whole exome or whole genome screening for patients with hypopituitarism

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Patient SAP

- Birth weight 3.6 kg, 38 weeks gestation
- 3 years, fell off growth curve in length and weight
  - GH provocative testing (GH max 1.4 mg/L)
  - Normal TFTs
  - MRI: pituitary hypoplasia
- Begun on GH
- Normal puberty

Younger sister diagnosed with GH deficiency

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Gli2

- Gli2 plays a role in sonic hedgehog signaling during embryogenesis
- Consists of four zinc fingers
- Mutations in Gli2 have been reported in hypopituitarism associated with CNS abnormalities and CPHD
- A Gli2 binding site is present on the GH promoter

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Gli2

- SAP found to have a novel heterozygous synonymous substitution in Gli2 by whole exome sequencing
- Results in a C535S amino acid substitution involving the Cys2His2 domain of the 4th zinc finger

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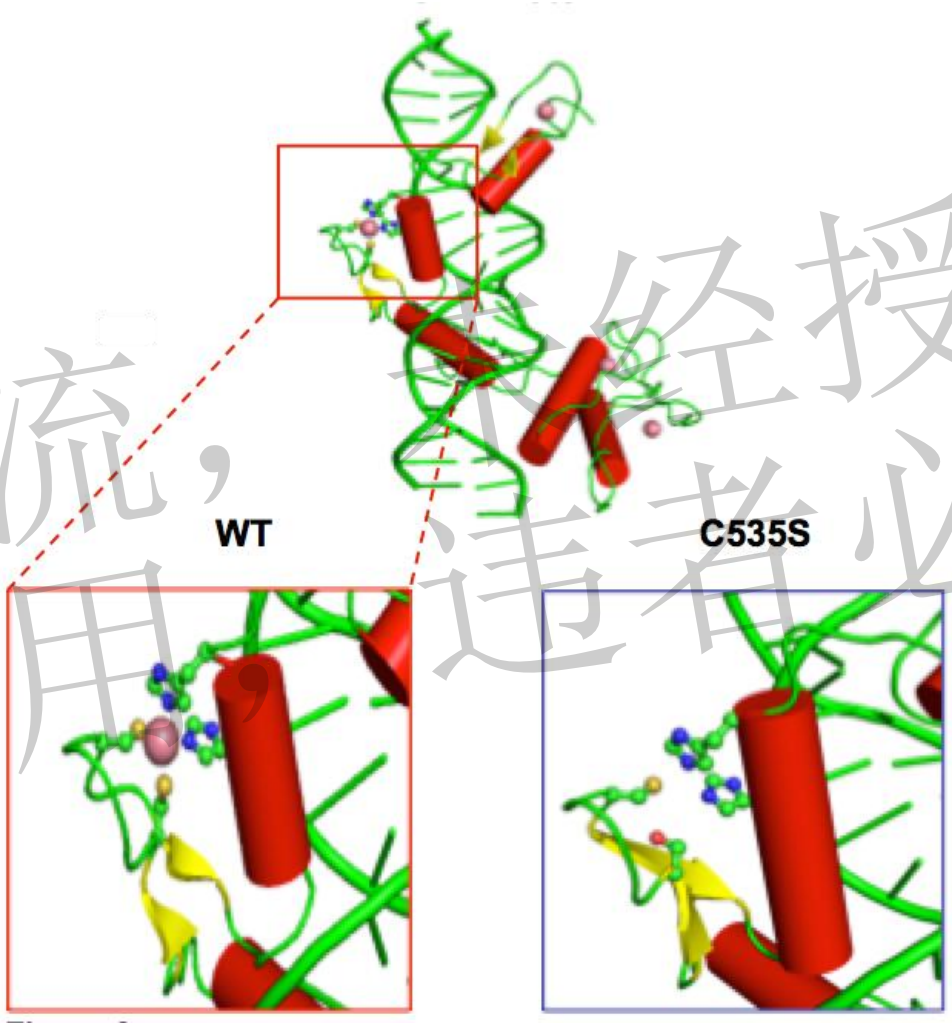
Gli2

An atomic level structural model using the SWISS-MODEL resource interactive modeling workspace of the Protein Model Portal



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Management of congenital hypopituitarism

- Who should be screened? How should they be screened?
  - All patients with congenital hypopituitarism should have a genetic evaluation, especially those with a family history and/or severe short stature
- When should they be screened?
  - Genetic screening should occur after the clinical diagnosis of hypopituitarism
- Which patients should be monitored for evolving hypopituitarism?
  - The phenotype for patients with some genetic forms of CPHD is evolving and unpredictable
  - Therefore, all patients with congenital hypopituitarism should have continued monitoring of pituitary function

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Why is a genetic diagnosis important?

- Prognostic implications for development of hormone deficiencies
  - Thus multiple hormone measurements are needed over time
- Timing of replacement therapy
- Genetic counselling
- Gene therapy

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Acknowledgements

- Support provided by NIH grant funding:
  - 4 - F32DK
  - 2 - T32DK
  - DRTC: P and F at U of C and JHU/UMD

- Collaborators:
  - The many endocrinologists who contributed patient samples
    - Andrew Wolfe, Ph.D.
    - Fredric Wondisford, M.D.
    - C. Ronald Kahn, M.D.
    - Rhonda Kineman, Ph.D.
    - Jens Bruning, Ph.D.
    - Jesus Argente
  - The National Institutes of Health
    - Gordon B. Cutler, M.D.
    - Amena Rahman, Ph.D.
    - Bruce Weintraub, M.D.
  - Children's Hospital, Boston
    - Laurie Cohen, M.D.
    - Thierry Brue, M.D.
    - Diego Botero, M.D.
    - Eric Su, M.D.
  - The University of Chicago
    - Ron Cohen, M.D.
    - Elizabeth Rochowitz, M.D.
    - Jennifer Robbins, M.S.
  - Johns Hopkins University School of Medicine
    - Christopher Romero, M.D.
    - Daniel Diaczok
    - Elyse Pine, M.D.
    - Kevin Shim, M.D, Ph.D.

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